REMARKS

Favorable reconsideration of this application is respectfully requested in view of the foregoing amendments and the following remarks.

Claims 96-99 having been added and claims 24-35, 37-43, 46-84 and 93-95 having been cancelled as directed to non-elected inventions, claims 1-23, 36, 44, 45, 85-92 and 96-99 are now pending in this application.

Claim 1 has been amended to specifically recite that TPO is thrombopoietin and EPO is erythropoietin. It is respectfully submitted that one skilled in the art would have understood the terms TPO and EPO in the first instance, however since the addition of the words thrombopoietin and erythropoietin do not affect the scope of claim 1, the amendment suggested in the Office Action is made herein. In addition, claims 91 and 92 are amended herein to change the reference to SEQ ID NO. 40 to SEQ ID NO. 39. SEQ ID NO. 40 is a nucleic acid sequence that encodes the amino acid sequence of SEQ ID NO. 39. It is respectfully submitted that from the context of claims 91 and 92 it would be clear to one skilled in the art that SEQ ID NO. 39 was originally intended.

With respect to the comments in the Office Action regarding the election of species, it is noted that claim 18 as presently amended recites an amino acid sequence "comprising" SEQ ID NO. 1 and therefore embraces the amino acid sequence of SEQ ID NO. 2 which is essentially SEQ ID NO. 1 having one additional amino acid (a proline) at one end. With respect to claims 20, 21, 91 and 92, it is respectfully noted that SEQ ID NO. 2 is included within at least one sequence specifically recited therein, see, e.g., SEQ ID NO. 39. Specifically, for example, SEQ ID NO. 39 includes the amino acid sequence of SEQ ID NO. 2 plus additional amino acids.

Thus, SEQ ID NO. 2 is in a sense generic to one or more embodiments embraced by the amino acid sequences specifically recited in claims 20, 21, 91 and 92. Accordingly, reconsideration of the withdrawal of claims 20, 21, 91 and 92 is respectfully requested.

Claims 1-16, 19, 22-23, 36, 44-45 and 85-90 have been rejected under 35 U.S.C. §112, second paragraph with respect to the appearance of the terms TPO and EPO. As noted above, while not necessarily agreeing with the basis for the rejection, since the suggested amendments do not alter the scope of the claims, those suggested amendments have been made, rendering this rejection moot.

Claims 4, 12, 14-16, 45 and 90 have been rejected under 35 U.S.C. §112, second paragraph. As far as Applicants understand the rejection, it appears that the examiner is unclear as to whether the same or different peptides are used in situations where at least a portion of two or more CDRs are replaced. It is respectfully submitted that the present amendments to the claims make clear that "the same or different peptides" can be used, thereby giving these claims their broadest scope and obviating this rejection.

Claims 85 – 89 also have been rejected under 35 U.S.C. §112, second paragraph because of a perceived inconsistency between claims 44 and 84. While not necessarily agreeing with the basis for the rejection, it is respectfully submitted that the present amendments render this rejection moot.

Claims 1-16, 19, 22-23, 36, 44-45 and 85-90 have been rejected under 35 U.S.C. §112, first paragraph. This rejection is respectfully traversed.

The pending claims are directed to immunoglobulin molecules or fragments thereof. Unquestionably, the specification includes a step by step description of suitable processes useful

in making the claimed immunoglobulins and includes detailed working examples of how to generate, select and test the activity of the claimed immunoglobulins. Beginning, e.g., on page 33 and continuing through page 36, Applicants' specification provides a detailed description of how to use antibodies prepared in accordance with the disclosure. Surely the level of detail provided in the specification would enable one skilled in the art to make and use the claimed immunoglobulins, whether a TPO mimetic, an EPO mimetic or any other biologically active peptide is used. Accordingly, withdrawal of the rejection of claims 1-16, 19, 22-23, 36, 44-45 and 85-90 under 35 U.S.C. §112, first paragraph is deemed appropriate and is respectfully requested.

Claims 1-16, 19, 22-23, 36, 44-45 and 85-90 have been rejected under 35 U.S.C. §103 as being obvious over Barbas et al. WO 94/18221 ("the Barbas PCT") in view of Dower et al WO 96/40750 ("Dower") and a 1995 article by Barbas et al. ("the Barbas article") and an article by Helms et al. ("Helms"). This rejection is respectfully traversed.

With respect to claim 1, the Barbas PCT application fails to disclose incorporation of a TPO or EPO mimetic into an immunoglobulin molecule as recited in claim1. Lacking any teaching of an EPO or TPO mimetic, the Barbas PCT application also fails to teach or suggest providing an amino acid sequence flanking a TPO or EPO mimetic within an immunoglobulin (see claim 2) or that a TPO or EPO mimetic should be flanked at its carboxy terminus with a proline within the immunoglobulin (see claim 3) or that two TPO or EPO mimetics can be incorporated into the an immunoglobulin (see claims 4 12 and 14) or that an immunoglobulin molecule containing an EPO or TPO mimetic can be a Fab fragment, $F(ab')_2$ fragment, ScFv fragment or a full IgG molecule (see claims 5 and 6), or that a TPO mimetic can be incorporated

into a CDR on the light chain of an immunoglobulin or the heavy chain of an immunoglobulin (see claims 7, 8 and 14), or that an EPO or TPO mimetic can be incorporated into an immunoglobulin heavy chain CDR3, CDR2 or both (see claims 9, 10 and 15), or that an EPO or TPO mimetic can be incorporated into an immunoglobulin light chain CDR1, CDR2, CDR2 or combinations thereof (see claims 11, 13 and 16), or where an amino acid sequence incorporated into the immunoglobulin is any of the specific sequences recited in any of claims 17 to 21, or where the EPO or TPO mimetic is incorporated into a human antibody, let alone a human anti-tetanus toxoid antibody (see claims 21 and 22).

Certain of these deficiencies are noted in the Office Action, others are not. For example, while it is acknowledged in the Office Action that the Barbas PCT application "...does not teach replacing a CDR with a TPO mimetic of SEQ ID NO:2...", there is no acknowledgement in the Office action that the Barbas PCT application does not teach incorporating ***any*** TPO mimetic into an immunoglobulin, let alone any of the 16 sequences specifically recited in claims 17-21, of which SEQ ID NO:2 is only one. Applicants understand that the Office Action focuses on SEQ ID NO:2 based on the election of species requirement that has been imposed, however the utter lack of any sequences in the Barbas PCT application related to the mimetics present in the invention presently recited in claim1 and all the claims that depend therefrom highlights that no prima facie case of obviousness is presented in the Office Action.

Rather than teach or suggest the incorporation of a TPO or EPO mimetic into an immunoglobulin molecule or fragment thereof, the Barbas PCT application contains a generic disclosure of incorporating a "binding site" into a CDR. Barbas's definition of "binding site" is "...any region of a protein or polypeptide that participates in protein-target molecule

interactions..." (See Barbas PCT at page 16 lines 22-28.) However, this generic definition which embraces ***millions*** of polypeptides provides no indication whatsoever that it is desirable, practical or even possible to incorporate the specifically recited EPO or TPO mimetics into an immunoglobulin molecule or fragment thereof. Even the further discussion of "binding site" in the first two paragraphs on page 20 the Barbas PCT application does not significantly limit the definition of binding site, but rather still suggests that the disclosed "binding site" can be one of over a million polypeptides (up to 50 amino acids with 14 choices at each location). Nothing in the definition of "binding site" would motivate one skilled in the art to consider the mimetics specifically recited in claim 1.

Nor do the specific "reference binding sites" listed in the first full paragraph on page 21 of the Barbas PCT application provide any indication that it is desirable, practical or even possible to incorporate the specifically recited EPO or TPO mimetics into an immunoglobulin molecule or fragment thereof. Specifically, examples of reference binding sites is provided at page 21 of the Barbas PCT application which states:

> "Exemplary reference binding sites are derived from the RGD-dependent integrin ligands, namely fibronectin, fibrinogen, vitronectin, von Willebrand factor and the like, from the envelope glycoprotein of viruses such as HIV gp120, EBV gp350/220, reovirus hemagglutinin, and the like, from cellular receptors such as CR2 or CD4, from protein hormones such as thyroid stimulating hormone (TSH), insulin, transferrin and the like, from apolipoproteins such as Apo E and Apo AI, from immunoglobulin CDRs, and from major histocompatibility complex class I or class II proteins."

Other examples of binding sites are provided at page 26 of the Barbas PCT application, which states:

> "5. Other Binding Sites

> Numerous other binding sites are contemplated by the present invention, and are readily obtainable the present screening methods. Preferred minimum recognition domains of binding sites for use in the invention are described below.
>
> The insulin receptor binding site on insulin has the amino acid residue sequence: RLFFNYLVIFEMVHLKE (SEQ ID NO 38).
>
> The reovirus receptor binding site on the viral hemagglutinin protein has the sequence: IVSYSGSGLN (SEQ ID NO 39).
>
> The fibrinogen receptor binding site on fibrinogen A alpha has the sequence: STSYDRGDS (SEQ ID NO 40).
>
> Thyroid hormone receptor has two preferred binding sites on thyroid stimulating hormone (TSH), and TSH has two forms. The TSHα binding site sequences are RSKKTML (SEQ ID NO 41) and ITSEAT (SEQ ID NO 42). The TSHB binding site sequences are NGKLFL (SEQ ID NO 43) and FSVPVALS (SEQ ID NO 44).
>
> The LDL receptor binding site on the Apo E protein has the sequence: $(LRX_1LRKRLLX_2)_2$ (SEQ ID NO 45), where X_1 can be K or A. and where X_2 can be R or A.
>
> The lipid A binding site has the sequence: IKTKKFLKKT (SEQ ID NO 46).
>
> The lecithin-cholesterol acyltransferase (LCAT) binding site on the Apo AI protein has the sequence: PYLLDFQKKWQEE (SEQ ID NO 47).
>
> The Mac-1 integrin receptor binding site on fibrinogen D-30 fragment has the sequence: QKRLDGS (SEQ ID NO 48)."

None of these specifically listed materials provides one skilled in the art any motivation to incorporate a TPO or EPO mimetic into an immunoglobulin molecule or fragment thereof.

In fact, at best, the Barbas PCT application may argruably make it obvious to try any one of the over a million polypeptides embraced by the definition of "binding site". However, it is hornbook patent law that "obvious to try" is not the appropriate standard for determining the obviousness of a claimed invention.

The Dower reference fails to cure all the above-noted deficiencies of the Barbas PCT application with respect to Applicants' claim 1. Specifically, Dower fails to disclose incorporation of a TPO or EPO mimetic into an immunoglobulin molecule as recited in claim1. Lacking any teaching of incorporating anything (let alone the recited EPO or TPO mimetics) into an immunoglobulin, Dower also fails to teach or suggest providing an amino acid sequence

flanking a TPO or EPO mimetic within an immunoglobulin (see claim 2) or that a TPO or EPO mimetic should be flanked at its carboxy terminus with a proline within the immunoglobulin (see claim 3) or that two TPO or EPO mimetics can be incorporated into the an immunoglobulin (see claims 4 12 and 14) or that an immunoglobulin molecule containing an EPO or TPO mimetic can be a Fab fragment, $F(ab')_2$ fragment, ScFv fragment or a full IgG molecule (see claims 5 and 6), or that a TPO mimetic can be incorporated into a CDR on the light chain of an immunoglobulin or the heavy chain of an immunoglobulin (see claims 7, 8 and 14), or that an EPO or TPO mimetic can be incorporated into an immunoglobulin heavy chain CDR3, CDR2 or both (see claims 9, 10 and 15), or that an EPO or TPO mimetic can be incorporated into an immunoglobulin light chain CDR1, CDR2, CDR2 or combinations thereof (see claims 11, 13 and 16), or where an amino acid sequence incorporated into the immunoglobulin is any of the specific sequences recited in any of claims 17 to 21, or where the EPO or TPO mimetic is incorporated into a human antibody, let alone a human anti-tetanus toxoid antibody (see claims 21 and 22).

The Dower disclosure is limited to low molecular weight peptides and peptide mimetics, and nowhere teaches or suggests that it is desirable, practical or even possible to incorporate the specifically recited EPO or TPO mimetics into an immunoglobulin molecule or fragment thereof. Specifically, at the paragraph bridging pages 4 and 5 Dower states:

> "This invention is directed, in part, to the novel and unexpected discovery that defined low molecular weight peptides and peptide mimetics have strong binding properties to the TPO-R and can activate the TPO-R. Accordingly, such peptides and peptide mimetics are useful for therapeutic purposes in treating conditions mediated by TPO (e.g., thrombocytopenia resulting from chemotherapy, radiation therapy, or bone marrow transfusions) as well as for diagnostic purposes in studying the mechanism of hematopoiesis and for the *in vitro* expansion of megakaroycytes and committed progenitor cells."

Being specifically limited to "defined *low molecular weight* peptides and peptide mimetics", Dower lacks any teaching with respect to immunoglobulin molecules or fragments that bears on the obviousness of claim 1 and the claims that depend therefrom.

Dower provides no motivation to incorporate the peptides and peptide mimetics disclosed therein into an immunoglobulin molecule or fragment thereof.

The rejection of claim 1 based on the Barbas PCT application in view of Dower is clearly an impermissible hindsight reconstruction of the claimed subject matter. There being no motivation to choose the specific peptide mimetics of Dower for use in the Barbas methods, it is only by using hindsight and Applicants' specification as a road map that it can even be alleged in the Office Action that an EPO or TPO mimetic should be incorporated into an immunoglobulin molecule or fragment thereof.

For all of the foregoing reasons, the Barbas PCT application does not, alone or in combination with Dower, render obvious claim 1 or any of the claims depending therefrom. Accordingly, the rejection of claims 1-23, 36 and 90 under 35 U.S.C. §103 is deemed appropriate and is respectfully requested.

Turning now to independent claim 44, nowhere does the Barbas PCT application teach or suggest an immunoglobulin molecule or fragment thereof comprising a region where amino acid residues corresponding to at least a portion of a CDR are replaced with a biologically active peptide flanked with a proline at the carboxy terminus of the biologically active peptide.

Although Barbas discloses the use of "regions of degeneracy", there is no appreciation that the presence of a proline at the carboxy terminus of the inserted biologically active peptide is

particularly useful compared to any other amino acid at that position. If it is the Examiner's position that Barbas specifically identifies a particular benefit in having a proline at the carboxy terminus of the inserted "binding site", the Examiner is respectfully requested to identify where in Barbas such teaching or suggestion can be found.

In contrast, it has been surprisingly found by Applicants that a proline flanking the peptide can provide an increase in biological activity. As reported at page three of Applicants' specification:

> "Thus, in one aspect, a biologically active peptide is provided with enhanced activity by adding a proline to its carboxy terminus to form a proline-extended biologically active peptide which is used to replace or add to at least a portion of at least one CDR region in an immunoglobulin molecule or fragment thereof. In another aspect, an immunoglobulin molecule or fragment thereof is provided which has either a TPO mimetic peptide or EPO mimetic peptide as a replacement for at least one native CDR region. In this aspect, the TPO mimetic peptide or EPO mimetic peptides may optionally be proline-extended as described herein."

It is these various proline-extended embodiments that are embraced by independent claim 44. The extensive data presented in the working examples of Applicants' support the conclusion that proline extension provides a beneficial and unexpected result. The conclusion supported by the data is summarized in the paragraph bridging pages 45 and 46 of Applicants' specification as follows:

> "All clones which demonstrated strong binding, were found to contain a proline just downstream of the 14 amino acid TPO mimetic peptide. Selection by panning of a proline in the downstream linker position represents determination of a surprising amino acid choice which confers improved binding characteristics to the grafted TPO mimetic peptide. Weak binders did not contain this proline although they still contained the TPO mimetic peptide."

Clearly, there is no appreciation in the Barbas PCT application that the presence of a proline at the carboxy terminus has any particular effect on the "binding site" inserted at a CDR.

Dower fails to cure all the above-noted deficiencies of the Barbas PCT application. Dower lacks any teaching with respect to immunoglobulin molecules or fragments that bears on the obviousness of claim 44 and the claims that depend therefrom. Applicants disagree with the statement at page 8 of the Office Action that "Dower et al teach ... the addition of flanking sequences for structural constraints...". Applicants have reviewed the cited page 9 of Dower and see no such teaching. In fact, a word search of the Dower text revealed no use of the word "flanking" by Dower and the appearance of the phase "structural constraints" only once at page 42 with respect to the inclusion of a carboxamide group or cyclic lactam at the carboxy terminus.

The Office Action expressly acknowledges, as it must, that Dower fails to teach a proline at the C-terminus. Lacking any teaching of a proline at the C-terminus, there cannot possibly be any appreciation in Dower that the presence of a proline at the C-terminus has any beneficial effect on the activity of a biologically active peptide that has been incorporated into an immunoglobulin molecule or fragment thereof.

For all of the foregoing reasons, the Barbas PCT application does not, alone or in combination with Dower, render obvious claim 44 or any of the claims depending therefrom. Accordingly, the rejection of claims 44, 45, 85, 87, 88 and 89 under 35 U.S.C. §103 is deemed appropriate and is respectfully requested.

While not necessarily agreeing with the balance of the statements on pages 9 and 10 of the Office Action regarding what would be obvious to one skilled in the art, in view of the foregoing discussion, it is believed that there is no need to address those specific comments at this time.

With respect to claims 86 and new claim 97-99, neither the Barbas PCT application nor Dower teach or disclose the use of a flanking sequence containing only 2 amino acids. The Barbas PCT application discloses regions of degeneracy having 3 to 20 amino acids. (See pages 29-30 of the Barbas PCT application). Dower lacks any teaching with respect to immunoglobulin molecules or fragments that bears on the obviousness of claims 86 and 97-99. In fact, it is not seen where in Dower there is any disclosure of the use of flanking amino acid sequences. Accordingly claims 86 and 97-99 are believed to be immediately allowable.

With respect to claim 96, it is admitted in the Office Action that neither the Barbas PCT application nor Dower teach a peptide comprising the sequence of SEQ ID NO:2. Accordingly claim 96 is believed to be immediately allowable.

In view of the foregoing amendments and remarks, this case is believed to be in condition for allowance. Such early and favorable action is earnestly solicited.

Respectfully submitted,

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